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COMPLETE SPECIFICATION

NO DRAWINGS

Pharmaceutical Compositions

We, NEISLER LABORATORIES INC., a corporation organized and existing under the laws of the State of Delaware, United States of America, and having a place of business at 434 North Morgan Street, Decatur, State of Illinois, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmaceutical compositions, particularly pharmaceutical compositions for oral administration in the form of capsules or tablets.

In the oral administration of certain therapeutically-active materials, it is often desirable to slow down release of the active ingredients into the gastro-intestinal tract, so that the material is absorbed at a more uniform rate. This permits a larger dose to be administered at any one time, which dose will produce a predetermined level of activity in the system for a relatively long period. Thus, an effective activity level may be maintained by administering a few capsules or tablets daily instead of a far greater number of small capsules at rigidly controlled time intervals.

It has previously been proposed to slow down the release of the active ingredients by providing layered capsules or tablets, the respective layers of which have variable disintegration rates. However, such capsules or tablets require careful compounding and they have not proved as effective in practice as was envisaged in theory. It has also been proposed to provide a tablet containing a substantial proportion of a neutral gum, such as methyl cellulose, guar gum or psyllium, utilizing the neutral gum's swelling and dispersing action to prolong the rate of distribution of the active ingredients into the stomach. Accurate and effective control of the rate of release of the therapeutic ingredients, utilizing such neutral gums, is difficult, since many factors affect the swelling and disintegration rates of the tablets. Another method for slowing down the rate of release of active materials from pharmaceutical compositions is to combine them with ion exchange resins to accomplish a degree of regulated release.

It is an object of the present invention to provide a pharmaceutical composition for oral administration in the form of a capsule or tablet containing an active ingredient which is slowly released at a fairly uniform rate and over a prolonged period when in the gastro-intestinal tract.

According to the present invention, a pharmaceutical composition for oral administration comprises a quantity of a therapeutically active material containing an organic amino group, in physical admixture with larger amounts up to 20 times its weight of a non-resinous non-toxic polycarboxylic acid compound which in the fluid of the digestive system exists as a complex with at least a portion of the therapeutically active material.

Representative examples of non-resinous, non-toxic polycarboxylic acid compounds which are capable of existing in the fluid of the digestive system as a complex with the active material are acids derived from pectin, for example, pectic acid and pectinic acid, and tannic acid. While we do not desire to be limited by a particular mechanism of action, it is believed that the effectiveness of the presently described tablet or capsule is due to an action of competition. Thus, when the active ingredient is combined with the free carboxylic acid compound in a tablet or capsule, and the same

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starts to disintegrate in the stomach, the carboxylic acid radicals will compete with the reactants in the stomach and intestine for the active ingredient. To clarify, when amphetamine phosphate, or other physiologically-active material is orally administered, it is absorbed into the human system from the stomach and intestinal tract. However, if free carboxylic acid groups are present, the active ingredient being reactive with the free carboxylic groups, a certain amount of the active ingredient will be taken on to the carboxylic acid-containing material to form a complex therewith. However, as the complex is exposed to the fluids in the digestive system and passes therethrough, it will be gradually decomposed to release the active ingredient into the system. It will thus be seen that a slow regulated absorption of the active material into the system is achieved.

Therapeutically-active ingredients which are suitable in the composition, capsule and/or tablet of the present invention are materials having a basic-reactive group in their chemical composition i.e., an amino group or ammonium group. Representative therapeutically-active ingredients include, for example, amphetamine, synephrine, antihistaminics of the normal dialkylaminoalkyl configuration, antispasmodics containing an amino group, hexamethonium bromide and related ammonium compounds, alkaloid material containing an amino group, Veratrum alkaloid, atropine and homatropine. If a basic amino group is present the active ingredient will afford sufficient basicity to be operative as above-described. The active ingredient may be employed, either as a free amine or as an acid addition salt. Quaternary ammonium salts are also operative, because they also are susceptible to the same mechanism of action.

Since the rate of release of the therapeutically-active ingredient is appreciably slowed down by the compounding as described by the present invention, rather larger amounts thereof than are normally used may be employed with safety utilizing the technique of the present invention. Therefore, there is little criticality in the amount of active ingredient which is employed. The release rate of the active ingredient is directly dependent upon the amount of polycarboxylic acid compound which is employed. As previously stated, the amount of the polycarboxylic acid compound must be greater than that of the active ingredient. We have found that when quantities greater than about twenty times the quantity of therapeutically-active ingredient of the polycarboxylic acid compound are employed, the rate of release is slowed down so considerably as to make the active ingredient substantially unavailable to the system. It is contemplated that six times the amount of polyanionic material based on the amount of active therapeutic ingredient constitutes an optimum amount thereof. A preferred embodiment of the present invention contemplates that a neutral gum having a swelling and dispersing action, such as, for example, methyl cellulose, guar gum, psyllium, locust bean gum, quince seed mucilage, linseed mucilage or Iceland Moss mucilage, will also be employed in conjunction with the two foregoing materials, to prevent an instant disintegration of the tablet upon administration. Since the competitive action hereinbefore described does not instantly take place, but rather takes some time, the inclusion of methyl cellulose allows the competitive action hereinbefore described to occur more effectively than when it is not included.

The amount of neutral gum employed will also affect the release rate of the active ingredient, and the amount employed will vary from about double that of the active ingredient used to approximately twenty times that amount of active ingredient used. It is also contemplated that conventional tableting materials, such as starch, sugar, dicalcium phosphate, calcium carbonate, magnesium carbonate, talcum, et cetera, may be added to the mixture to give desired size, bulk, color, texture, buffering et cetera.

A specific non-limitative example of a composition of the present invention comprises:

Example

d-amphetamine dibasic phosphate	0.08 grains
pectic acid	0.5 grain
methyl cellulose	2.0 grains
starch	0.5 grain

This mixture is intimately mixed and run in a conventional type tableting machine to punch a tablet. Thereafter, a coating of 2.5 grains of caffeine was added thereto. The result was an appetite-depressant and mood-elevation agent having an effective time up to about six hours.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition for oral administration comprising a quantity of a therapeutically active material containing an organic amino group, in physical admixture with larger amounts up to 20 times its weight of a non-resinous non-toxic polycarboxylic acid compound which in the fluid of the digestive system exists as a complex with at least a portion of the therapeutically active material.

2. A pharmaceutical composition according to claim 1 wherein the polycarboxylic acid compound is tannic acid.

3. A pharmaceutical composition accord-

ing to claim 1 wherein the polycarboxylic acid compound is an acid derived from pectin.

4. A pharmaceutical composition according to any of claims 1, 2 or 3 wherein the polycarboxylic acid compound is present in an amount about 6 times by weight the amount of therapeutically active material.

5. A pharmaceutical composition according to any of the preceding claims wherein the therapeutically active material is a *d*-amphetamine salt.

6. A pharmaceutical composition according to any of the preceding claims containing from 2-20 times the weight of active ingredient of a neutral gum.

7. A pharmaceutical composition substantially as described with reference to the Example.

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